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APPELLANTS' BRIEF		
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	First Named Inventor	John W. Adams
Address to: Mail Stop Appeal Brief-Patents Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner	Ruixiang Li
	Group Art	1646
	Title: Human G Protein-Coupled Receptor and Modulators Thereof for the Treatment of Cardiovascular Disorders	

Sir:

This Brief is filed in support of Appellants' appeal from the Final Rejection dated March 2, 2011. Claims 136-143 and 156-163 are rejected and are appealed herein. A Notice of Appeal was filed on March 15, 2011 making this Brief due by May 15, 2011. Accordingly, this Appeal Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134(a).

The Commissioner is hereby authorized to charge deposit account number 50-0815, reference no. AREN-060 to cover any required fee for filing the Appellants' brief. Additionally, in the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to the above disclosed account.

TABLE OF CONTENTS

REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights to the invention to Arena Pharmaceuticals, Inc.

RELATED APPEALS AND INTERFERENCES

There are currently no other appeals or interferences known to Appellants, the undersigned Appellants' representative, or the assignee to whom the inventors assigned their rights in the instant case, which would directly affect or be directly affected by, or have a bearing on the Board's decision in the instant appeal.

STATUS OF CLAIMS

Claims 1-135 and 155 are canceled.

Claims 136-154 and 156-163 are pending.

Claims 144-154 are withdrawn from consideration.

Claims 136-143 and 156-163 stand rejected and are appealed herein.

STATUS OF AMENDMENTS

No amendments to the claims were filed subsequent to issuance of the Final Rejection.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 136 provides a method of identifying a compound capable of inhibiting cardiomyocyte hypertrophy. This method comprises:

(a) contacting a candidate compound with a host cell or an isolated membrane thereof comprising a recombinant G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2, wherein said G protein-coupled receptor has constitutive activity (page 5, lines 14-21; page 5 lines 21-27; page 6 lines 8-12; page 7 line 21 page 11 lines 9-12);

(b) determining that the compound inhibits signaling by said G protein-coupled receptor (page 6 lines 8-12), and

(c) determining if the compound inhibits hypertrophy of a myocardial cell (page 12 lines 24-27).

Claim 160 provides a method of identifying a compound capable of inhibiting

cardiomyocyte hypertrophy. This method comprises:

(a) contacting a candidate compound with a host cell or an isolated membrane thereof comprising a recombinant G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2, wherein said G protein-coupled receptor has constitutive activity (page 5, lines 14-21; page 5 lines 21-27; page 6 lines 8-12; page 7 line 21' page 11 lines 9-12);

(b) identifying the candidate compound as a compound that inhibits signaling by said G protein coupled receptor (page 6 lines 8-12); and

(c) obtaining a determination that the compound identified in (b) inhibits hypertrophy of a mycocardial cell (page 12 lines 24-27).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 136-143, 156-163 are rejected as not meeting the written description requirement of 35 U.S.C. § 112, first paragraph. This is a new matter rejection .

II. Claims 136-143, 156-163 are rejected as not meeting the enablement requirement of 35 U.S.C. § 112, first paragraph.

III. Claims 160-163 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

ARGUMENT

I. Claims 136-143, 156-163 are rejected as not meeting the written description requirement of 35 U.S.C. § 112, first paragraph.

On page 3 of the Office Action, the Examiner recites element (a) of claim 136 (i.e., "contacting a candidate compound with a host cell or an isolated membrane thereof comprising a recombinant G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2, wherein said G protein-coupled receptor has constitutive activity") and then states that the element "introduces *new matter*" (emphasis added). As such, this rejection is read as being a new matter rejection.

The Examiner argues that the element adds new matter because "there is no requirement of the GPCR used in the method to be overexpressed in cardiomyocytes. Thus, the subject matter in the amendment is broader than disclosed in the specification." See the second full paragraph on page 3. In dismissing the Appellants' earlier arguments, the Examiner states exactly the same thing, i.e., "there is no requirement of the GPCR used in the method to be overexpressed in cardiomyocytes. Thus, the subject matter in the amendment is broader than disclosed in the specification". See first paragraph on page 4.

As best understood by the Appellants, this rejection appears to be based on the Examiner's assertion that the specification only describes the use of cardiomyocytes that overexpress a GPCR and, as such, any claims that are broader than that include new matter.

However, the specification is not limited in the way that the Examiner argues. For example, the description of a screening assay found on ¶80 on page 19 is not limited to one in which cardiomyocytes that overexpress a GPCR are used. Likewise, none of the original claims of the application are limited to the use of cardiomyocytes that overexpress a GPCR. Finally, ¶114 of the specification provides a non-limiting list of non-cardiomyocyte host cells that can be employed in the method, (i.e., "In some embodiments, the host cell is mammalian and selected from the group consisting of 293, 293T, CHO and COS-7.").

In view of the above, the Appellants submit that the Examiner has no basis for arguing that the claims are broader than disclosed in the specification.

Reversal of this rejection is therefore requested.

II. Claims 136-143, 156-163 are rejected as not meeting the enablement requirement of 35 U.S.C. § 112, first paragraph.

Claims 136-143, 156-163 are rejected under 35 U.S.C § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for performing a method using a GPCR (G protein-coupled receptor) comprising an amino acid sequence that is at least 95% identical to SEQ ID NO:2. Appellants traverse.

Claims 136 and 160, from which all rejected claims depend, are directed to a screening method that employs a G protein-coupled receptor (GPCR) comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2. The basis for this rejection relates in large part to the claims encompassing variants of the human, mouse and rat RUP40 GPCR sequences that are explicitly disclosed in the specification. The question is whether one of skill in the art would make and use such molecules without undue experimentation.

The law relating to enablement is well established.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claim is not adequately enabled by the description of the invention provided in the specification of the application.

In re Wright, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993)

> "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive'".

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of hot to practice a desired embodiment of the invention claimed.

PPG Indus., 75 F.3d 1564 (quoting *Ex parte Jackson* 217 USPQ 804 807 (BPAI 1982))

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1998).

In making this rejection, the Examiner argues that variants of SEQ ID NO:2 are not enabled because "it is unpredictable whether a GPCR that has 95% sequence identity to SEQ ID NO: 2 shares the same property of RUP40 GPCR of SEQ ID NO:2 because the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of GPCR variants and homologs. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function". See OA page 8, 1st ¶.

However, predictability is but one of the factors in the Wand's analysis. The crux of the question of enablement is whether, taking all the Wand's factors into account, practice of the claimed method would require undue experimentation.

The specification discloses the sequence of a wild type human RUP40 (SEQ ID NO:2), as well as the sequence of wild type rat RUP40 (SEQ ID NO:4) and the partial sequence of wild type mouse RUP40 (SEQ ID NO:6). RUP40 fusion proteins are described throughout the specification. See, e.g., pages 95-97. The specification also teaches that several techniques for making variants, e.g., by site-directed mutagenesis, PCR or direct synthesis, were generally available at the time of filing. See ¶390 on page 80 and ¶¶410 and 411 on page 90. The specification states that RUP40 is a GPCR that is coupled to Gq and increases the production of IP_3 when stimulated, as evidenced by substantial constitutive activity (see Fig. 5, for example). See, e.g., ¶14 on page 4, ¶553 on page 133 and Fig. 5. The specification describes the general structure/function relationship of GPCRs. See, e.g, ¶5 on page 2 to ¶13 on page 4. The specification describes a variety of methods for assaying GPCRs which can be used to test variant proteins for activity. See the section starting on page 93 as well as page 132. The specification also describes working examples showing that elevated RUP40 activity in cardiomyocytes through recombinant expression of constitutively active wild type human RUP40 leads to hypertrophy of myocardial cells and an increase in atrial natriuretic factor (ANF) expression. See Example 15 on page 13 and Figs. 6A and 6B.

In particular, the specification discloses the sequence of human RUP40, rat RUP40 and partial mouse RUP40. Because the proteins defined by these sequences are functional orthologs, the sequences can be cross-compared to identify amino acid positions that are tolerant to substitution, as well as amino acid positions that may not be tolerant to substitution. This information can be used to generate variants of human RUP40 that would be expected to be functional. For example, amino acids 991 to 1,346 of SEQ ID NO:2 (human RUP40) correspond to amino acids 994 to 1,349 of SEQ ID NO:4 (rat RUP40). Comparison of these sequences indicates they differ at 51 positions, and that they are *85.7%* identical. Therefore, in making a variant of the human RUP40 for use in the claimed method, one of skill in the art would be able to make amino acid substitutions at up to 17 of any of the 51 differing positions without expecting a loss of activity.

Moreover, the record shows that RUP40 is a member of an extremely well characterized family of proteins: the GPCRs. A search of NCBI's PubMed database reveals that there are well over 3700 journal articles, including 614 reviews, that have a publication date that precedes the priority date of the instant application (June 20, 2003) and contain the phrase "GPCR" OR "G protein-coupled receptor" in the abstract. See Exhibit A. Thus, at the priority date of the instant application, GPCR proteins were a subject of significant interest in the scientific community, and the level of skill in the art was very high. The art in which the subject RUP40 protein belongs was therefore highly developed at the priority date of the instant application.

For example, at the priority date of the instant application one of skill in the art would have knowledge of the atomic coordinates of at least one GPCR (see, e.g., Palczewski 2000; full citation and reference provided in evidence appendix). At the time of filing, the structure/function relationship of many GPCRs had been investigated (see, e.g., Shin 2002, Chung 2002, Mouledous 2000, Krasnoperoc 1999, Hurley 1999, Akal-Strader 2002, and Yang 2002; full citation and references provided in evidence appendix), and several reviews on the structure/function relationship of GPCRs had been published (see, e.g., Ulloa-Aguirre 1999, Chollet 1999, Gimpl 2001, Bai 1999, Olah 2000, Missale 1998 and Sealfon 1995; full citation and references provided in evidence appendix). In addition, at the time of filing, one of skill in the art would have been aware of several algorithms for

predicting GPCR structure (see, e.g., Filizola 1998 and Orry 2000; full citation and references provided in evidence appendix), an algorithm for predicting important residues in GPCRs (see, e.g., Califano 2000; full citation and reference provided in evidence appendix), and reviews on the engineering of GPCRs by domain swapping (see, e.g., Gouldson 1998 and Gouldson 2000; full citation and references provided in evidence appendix). These references are all of record in the instant case.

Given the information in the instant specification and the deep general understanding of the structure and function of GPCR proteins, the Appellant submits that one of skill in the art would be able to make and use a large number of operable variants of RUP40 without undue experimentation.

The Appellants' arguments for withdrawal of the outstanding rejection are consistent with *Ex parte Kubin* (BPAI 2007; Appeal no. 2007-0819) which is a *precedential* decision by the BPAI. The grounds of the enablement rejection decided in *Ex parte Kubin* are similar to the grounds of rejection in the instant case in that in *Ex parte Kubin* a claim reciting "80% identity" language[1] was rejected as being non-enabled because there were no working examples other than SEQ ID NOS:1 and 2, and because very small changes in sequence, even one amino acid, can alter protein function. In this case, the Board acknowledged that although biotechnology is unpredictable, the other Wands factors, particular "the state of the art" and "the relative skill of those in the art" weigh more heavily in the Appellants' favor. In essence, the Board in *Ex parte Kubin* stated that "The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art". Given the evidence described above and applying the logic of *Ex parte Kubin*, the Appellants submit that practice of the claimed method would not require undue experimentation, and this rejection should be withdrawn.

The Appellants also note that the BPAI has reversed several rejections based on similar grounds to those of this rejection. For example, in *Ex parte Liao* (BPAI

[1] Claim 73, the independent claim discussed in *Ex parte Kubin* recites: "An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48".

2008; Appeal No. 2008-4364) the claims[2] were rejected because the specification did not identify any domain of EDG-1 that was critical for EDG-1 activity. Like RUP40, EDG-1 is a GPCR. In this case, the Board recognized that the effect of amino acid substitutions can be unpredictable. However, the rejection was reversed because although one of skill in the art might have been required to make and test every EDG1 variant encompassed by the claims, the claims were nevertheless enabled because the level of skill in the art is high (particularly because EDG-1 is a GPCR) and the experimentation would have been routine. Likewise, in *Ex parte Heck* (BPAI 2008; Appeal No. 2008-28753), the Board noted that "some deletions and mutations will reduce activity". However, the Board reversed the rejection because "the amount of experimentation to practice the full scope of the claimed invention might be extensive, such experimentation would have been routine." Similarly, in *Ex parte Abad* (BPAI 2007; Appeal No. 2007-43564), the Board again noted "any particular mutation in a protein sequence, even a conservative mutation, may result in an unpredictable change in the activity or function of a particular protein". In this case, the Board reversed the rejection because identifying active variants "would have required some experimentation in order to determine which nucleic acids would have pesticide activity and against which pests, but that experimentation would have been routine, not undue".

The Appellants understand that every case has its own set of facts that distinguishes that case from others. However, given the guidance in the instant specification, the vast amount of structural information on GPCRs available in the prior art, the similarity of this case to the cases discussed in *Ex Parte Kubin*, *Ex parte Liao*, *Ex parte Heck* and *Ex parte Abad*, and the limited scope of the claims, which recite structural and functional parameters for the sequences used in the claimed method, the Appellants believe that one of skill in the art would be able to practice the claimed method without undue experimentation. As such, this rejection should be reversed.

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[2] The claims appealed in this case were directed to a screening method that employed a polypeptide "having at least 95% identity to an amino acid sequence of SEQ ID NO:5".
[3] The claims appealed in this case were directed to an isolated polynucleotide that is "at least about 98% identity" to SEQ ID NO:1.
[4] The claims appealed in this case were directed to an isolated nucleotide acid "having at lest 90% sequence identity to" SEQ ID NO:3, wherein the sequence encodes a pesticidal polypeptide.

As explained in greater detail below, the Examiner makes a number of erroneous statements in the Office Action. In view of these erroneous statements, the Appellants submit that the basis for the rejection lacks foundation.

On page 6 of the Office Action, the Examiner states that that "human RUP40 is not disclosed as being constitutively active." However, as explained in ¶553 of the specification (on page 133), human RUP40 (SEQ ID NO:2; see ¶550) "manifested a level of constitutive Gq coupling activity", as evidenced by the IP_3 accumulation assay described in Example 14 of the application. As such, the specification explicitly discloses that wild type human RUP40 is constitutively active. This conclusion is consistent with the results discussed in Example 15, which show that that wild type RUP40 causes a cellular phenotype if it is expressed in a cell. The Examiner's argument that human RUP40 is not disclosed as being constitutively active is therefore inconsistent with the data shown in the instant application, and carries no weight.

Likewise, on page 6 of the Office Action, the Examiner contends that "without a known ligand/agonist of overexpression of the human RUP40 in cardiomyocytes, one skilled in the art would not be able to identify a compound that inhibits the signaling of human RUP40 and inhibits cardiomyocyte hypertrophy." However, the specification teaches that wild type human RUP40 exhibits constitutive activity, such as when recombinantly expressed in a host cell, e.g. a cardiomyocyte. An inhibitor of constitutive activity can be identified in the absence of a known ligand/agonist of the receptor. An exemplary inhibitor is an inverse agonist. An identified inhibitor can subsequently be assayed for inhibition of hypertrophy in a myocardial cell. The Examiner's argument that a known ligand or agonist is required to identify an inhibitor of signaling by human RUP40 is therefore inconsistent with the data shown in the instant application, and carries no weight. The Examiner may not know what an inverse agonist is (see, e.g., ¶360).

Finally, on page 7 of the Office Action, the Examiner argues that "inhibiting cardiomyocyte hypertrophy may be determined in a cardiomyocyte cell, *not any kind of cell as recited in the claims*" (emphasis added). However, claim 136 and 160 require compounds that inhibit hypertrophy of *myocardial* cells. See claim 136:

"determining if the compound inhibits hypertrophy of a *myocardial* cell" (emphasis added) and claim 160 requires "obtaining a determination that the compound identified in (b) inhibits hypertrophy of a *myocardial* cell" (emphasis added). Recitation of myocardial cell can be found throughout the specification (see, e.g., ¶¶3 and 16) Because these claims require a *myocardial* cell, rather than "any kind of cell", the Examiner's statement is inaccurate.

In view of the above, the Appellants submit that the Examiner has made a number of errors in attempting to establish this rejection.

The Appellants submit that this rejection has been adequately addressed. Withdrawal of this rejection is requested.

III. Claims 160-163 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

This rejection, as found on page 10 of the Office Action, is pasted below.

> Claim 160 is indefinite because it recites a limitation in step (c). "obtaining a determination that the compound identified in (b) inhibits hypertrophy of a myocardial cell". It is unclear what the metes and bound of the limitation is. Claims 161-163 are rejected as dependent claims from claim 160.

This rejection should be reversed because the rejection does not explain why the phrase in question is indefinite.

To the extent that any further discussion is necessary, the Appellants submit that because the claim starts with a verb i.e., "obtaining" and then sets forth what is being obtained, i.e., "a determination that that the compound identified in (b) inhibits hypertrophy of a myocardial cell", it is not clear to the Appellants how such a phrase can be indefinite, particularly since ways in which compounds can be tested to determine if they inhibit hypertrophy of a myocardial cell are well known and examples of which are found throughout the application. See, e.g., the section starting on page 93, page 132 and Example 15 on page 133.

The Appellants submit that there is no basis for this rejection. Reversal of this rejection is requested.

In view of the foregoing discussion, the Appellants contend that a *prima facie* case of obviousness cannot be maintained and respectfully request that the rejections be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: April 19, 2011

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

CLAIMS APPENDIX

136. A method of identifying a compound capable of inhibiting cardiomyocyte hypertrophy, comprising:

(a) contacting a candidate compound with a host cell or an isolated membrane thereof comprising a recombinant G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2, wherein said G protein-coupled receptor has constitutive activity;

(b) determining that the compound inhibits signaling by said G protein-coupled receptor, and

(c) determining if the compound inhibits hypertrophy of a myocardial cell.

137. The method of claim 136, wherein element (c) comprises:

(i) contacting the compound with a cardiomyocyte cell *in vitro*; and

(ii) determining whether the compound inhibits hypertrophy of the cardiomyocyte cell.

138. The method of claim 137, wherein the method comprises measuring the size of the cardiomyocyte cell or the expression of atrial natriuretic factor (ANF) by the cardiomyocyte cell.

139. The method of claim 136, wherein element (c) comprises:

(i) administering the compound to a mammal; and

(ii) determining whether the compound inhibits hypertrophy of the heart of the mammal.

140. The method of claim 139, wherein the mammal is a rat, a mouse or a pig.

141. The method of claim 139, wherein element (ii) comprises evaluating congestive heart failure, congestive cardiomyopathy, heart hypertrophy, left ventricular hypertrophy, right ventricular hypertrophy or hypertrophic cardiomyopathy.

142. The method of claim 136, wherein the method comprises identifying an inverse agonist of the receptor.

143. The method of claim 136, wherein the method comprises identifying an antagonist of the receptor.

156. The method of claim 139, wherein element (ii) comprises evaluating hypertrophy of the heart in congestive heart failure or congestive cardiomyopathy.

157. The method of claim 139, wherein element (ii) comprises evaluating hypertrophy of the heart in post-myocardial infarction re-modeling.

158. The method of claim 136, wherein the signaling is production of a reporter protein by a cell.

159. The method of claim 136, wherein said signaling is production of IP_3 in a cell.

160. A method of identifying a compound capable of inhibiting cardiomyocyte

hypertrophy, comprising:

(a) contacting a candidate compound with a host cell or an isolated membrane thereof comprising a recombinant G protein-coupled receptor comprising an amino acid sequence having at least 95% identity to amino acids 991 to 1,346 of SEQ ID NO:2, wherein said G protein-coupled receptor has constitutive activity;

(b) identifying the candidate compound as a compound that inhibits signaling by said G protein coupled receptor; and

(c) obtaining a determination that the compound identified in (b) inhibits hypertrophy of a myocardial cell.

161. The method of claim 160, wherein the method comprises identifying an inverse agonist of the receptor.

162. The method of claim 160, wherein the signaling is production of a reporter protein by a cell.

163. The method of claim 160, wherein said signaling is production of IP3 in a cell.

EVIDENCE APPENDIX

The following exhibit and references were made of record in a response and IDS that was filed by the Appellants on November 30, 2009. The Examiner indicated that all of the references were considered on January 22, 2010.

Exhibit A.

A. Palczewski et al. *Crystal structure of rhodopsin: A G protein-coupled receptor.* Science 2000 289:739-45.

B. Shin N et al. *Molecular modeling and site-specific mutagenesis of the histamine-binding site of the histamine H4 receptor.* Mol Pharmacol. 2002 62:38-47.

C. Chung DA et al. *Mutagenesis and peptide analysis of the DRY motif in the alpha2A adrenergic receptor: evidence for alternate mechanisms in G protein-coupled receptors.* Biochem Biophys Res Commun. 2002 293:1233-41.

D. Mouledous et al. *Functional inactivation of the nociceptin receptor by alanine substitution of glutamine 286 at the C terminus of transmembrane segment VI: evidence from a site-directed mutagenesis study of the ORL1 receptor transmembrane-binding domain.* Mol Pharmacol. 2000 57:495-502.

E. Krasnoperov et al. *Structural requirements for alpha-latrotoxin binding and alpha-latrotoxin-stimulated secretion. A study with calcium-independent receptor of alpha-latrotoxin (CIRL) deletion mutants.* J Biol Chem. 1999 274:3590-6.

F. Hurley et al. *Structure-function studies of the eighth hydrophobic domain of a serotonin receptor.* J Neurochem. 1999 72:413-21

G. Akal-Strader et al. *Residues in the first extracellular loop of a G protein-coupled receptor play a role in signal transduction.* J Biol Chem. 2002 277:30581-90.

H. Yang et al. *Molecular determinants of human melanocortin-4 receptor responsible for antagonist SHU9119 selective activity.* J Biol Chem. 2002 277:20328-35

I. Ulloa-Aguirre et al. *Structure-activity relationships of G protein-coupled receptors.* Arch Med Res. 1999 30:420-35 (Review)

J. Cholet et al. *Biophysical approaches to G protein-coupled receptors: structure, function and dynamics.* J Comput Aided Mol Des. 1999 13:209-19 (Review)

K. Gimpl et al. *The oxytocin receptor system: structure, function, and regulation.* Physiol Rev. 2001 81:629-83 (Review)

L. Bai et al. *Structure and function of the extracellular calcium-sensing receptor.* Int J Mol Med. 1999 4:115-25 (Review)

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N. Missale et al. *Dopamine receptors: from structure to function.* Physiol Rev. 1998 78:189-225 (Review)

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P. Filizola et al. *BUNDLE: a program for building the transmembrane domains of G-protein-coupled receptors.* J Comput Aided Mol Des. 1998 12:111-8.

Q. Orry et al. *Modeling and docking the endothelin G-protein-coupled receptor.* Biophys J. 2000 79:3083-94.

R. Califano *SPLASH: structural pattern localization analysis by sequential histograms.*

Bioinformatics. 2000 16:341-57.

S. Gouldson et al, *Domain swapping in G-protein coupled receptor dimers*. Protein Eng. 1998 11:1181-93.

T. Gouldson et al, *Dimerization and domain swapping in G-protein-coupled receptors: a computational study*. Neuropsychopharmacology. 2000 23:S60-77.